Practitioner's Docket No. 56687 (71526)

CHAPTER II

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US) (ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

PCT/JP00/04361	30 June 2000	01 July 1999
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED

ADHESIVE PREPARATION FOR PERCUTANEOUS ABSORPTION
TITLE OF INVENTION

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APPLICANTS

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

NOTE: To avoid abandonment of the application, the applicant shall furnish to the USPTO, not later than 20 months from the priority date: (1) a copy of the international application, unless it has been previously communicated by the International Bureau or unless it was originally filed in the USPTO; and (2) the basic national fee (see 37 C.F.R. § 1.492(a)). The 30-month time limit may not be extended. 37 C.F.R. § 1.495.

WARNING: Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. §1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing - See 37 C.F.R. §1.8.

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 USC 371 otherwise the submission will be considered as being made under 35 USC 111. 37 C.F.R. § 1.494(f).

CERTIFICATION UNDER 37 C.F.R. § 1.10*
*(Express Mail label number is **mandatory**.)*
(Express Mail certification is optional.)

I hereby certify that this paper, along with any document referred to, is being deposited with the United States Postal Service on this date December 31, 2001, in an envelope as "Express Mail Post Office to Addressee," mailing Label Number **EL932648533US**, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Susan M Dillon
(type or print name of person mailing paper)

Susan M. Dillon
Signature of person mailing paper

WARNING: Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.

WARNING: Each paper or fee filed by "Express Mail" **must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

1. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. 371:

   a. [X] This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

   b. [X] The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2. Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
[ ]*	TOTAL CLAIMS	6 - 20 =	0	x $ 18.00 =	$0
	INDEPENDENT CLAIMS	1 - 3 =	0	x $ 84.00 =	$0
	MULTIPLE DEPENDENT CLAIM(S) (if applicable) + $270.00				$280.00
BASIC FEE**	[ ] U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: [ ] and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(2) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 CFR 1.492(a)(4)) ..... . $100.00 [ ] and the above requirements are not met (37 CFR 1.492(a)(1)) ..... $710.00 [X] U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the USPTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: [ ] has been paid (37 CFR 1.492(a)(2)) ..... $740.00 [ ] has not been paid (37 CFR 1.492(a)(3)) ..... $1040.00 [X] where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5))..... $890.00				$890.00
	Total of above Calculations				= $1,170.00
SMALL ENTITY	Reduction by ½ for filing by small entity, if applicable. Affidavit must be filed. (note 37 CFR 1.9, 1.27, 1.28)				- $
	Subtotal				$1,170.00
	Total National Fee				$1,170.00
	Fee for recording the enclosed assignment document $40.00 (37 CFR 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				$
TOTAL	Total Fees enclosed				$1,170.000

   i. [X] A check in the amount of $1,170.00 to cover the above fees is enclosed.

   ii. [ ] Please charge Account No. _____ in the amount of $ _____.

A duplicate copy of this sheet is enclosed.

**WARNING: *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. [X] A copy of the International application as filed (35 U.S.C. 371(c)(2)):

NOTE: *Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.*

a. [ ] is transmitted herewith.
b. [ ] is not required, as the application was filed with the United States Receiving Office.
c. [X] has been transmitted
   i. [X] by the International Bureau.
   Date of mailing of the application (from form PCT/IB/308):**11 January 2001**
   ii. [ ] by applicant on _____.
   Date

4. [X] A translation of the International application into the English language (35 U.S.C. 371(c)(2)):
   a. [X] is transmitted herewith.
   b. [ ] is not required as the application was filed in English.
   c. [ ] was previously transmitted by applicant on _____.
   Date
   d. [ ] will follow.

5. [X] Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. 371(c)(3)):

NOTE: *The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.*

a. [ ] are transmitted herewith.
b. [ ] have been transmitted
   i. [ ] by the International Bureau.
   Date of mailing of the amendment (from form PCT/IB/308): _____.

ii. [ ] by applicant on _____.
Date

c. [X] have not been transmitted as
i. [X] applicant chose not to make amendments under PCT Article 19.
Date of mailing of Search Report (from form PCT/ISA/210): **Oct. 3, 2000**
ii. [ ] the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. [X] A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. 371(c)(3)):
a. [ ] is transmitted herewith.
b. [ ] is not required as the amendments were made in the English language.
c. [X] has not been transmitted for reasons indicated at point 5(c) above.

7. [X] A copy of the international examination report (PCT/IPEA/409)
[X] is transmitted herewith.
[ ] is not required as the application was filed with the United States Receiving Office.

8. [X] Annex(es) to the international preliminary examination report
a. [X] is/are transmitted herewith.
b. [ ] is/are not required as the application was filed with the United States Receiving Office.

9. [ ] A translation of the annexes to the international preliminary examination report
a. [ ] is transmitted herewith.
b. [ ] is not required as the annexes are in the English language.

10. [X] An oath or declaration of the inventor (35 U.S.C. 371(c)(4)) complying with 35 U.S.C. 115
a. [ ] was previously submitted by applicant on _____.
Date
b. [ ] is submitted herewith, and such oath or declaration
i. [ ] is attached to the application.
ii. [ ] identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. 1.70.
iii. [X] will follow.

Other document(s) or information included:

11. [X] An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):
a. [X] is transmitted herewith.
b. [ ] has been transmitted by the International Bureau.
Date of mailing (from form PCT/IB/308): _____.
c. [ ] is not required, as the application was searched by the United States International Searching Authority.
d. [ ] will be transmitted promptly upon request.

e. [ ] has been submitted by applicant on _____.
Date

12. [X] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98:
a. [X] is transmitted herewith.
Also transmitted herewith is/are:
[X] Form PTO-1449 (PTO/SB/08A and 08B).
[X] Copies of citations listed.
b. [ ] will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).
c. [ ] was previously submitted by applicant on _____.
Date

13. [ ] An assignment document is transmitted herewith for recording.

A separate [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [ ] FORM PTO 1595 is also attached.

_____
_____
_____

14. [X] Additional documents:
a. [X] Copy of request (PCT/RO/101)
b. [X] International Publication No. WO 01/01990
i. [X] Specification, claims and drawing
ii. [ ] Front page only
c. [ ] Preliminary amendment (37 C.F.R. § 1.121)
d. [X] Other

Article 34 Amendment and English language translation
PCT/RO/105
PCT/ISA/202
PCT/IB/301
PCT/IB/304
PCT/IB/308
PCT/IB/332
PCT/IPEA/401
PCT/IPEA/402
PCT/IPEA/408
PCT/IPEA/416
Reply to Written Opinon

15. [X] The above checked items are being transmitted
a. [X] before 30 months from any claimed priority date.
b. [ ] after 30 months.

16. [ ] Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____, namely:

_____
_____

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: *"A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).*

NOTE: *"Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).*

[X] The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. **04-1105.**

[X] 37 C.F.R. 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

[X] 37 C.F.R. 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: *Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.*

[X] 37 C.F.R. 1.17 (application processing fees)
[X] 37 C.F.R. 1.17(a)(1)-(5)(extension fees pursuant to § 1.136(a).
[ ] 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b))

NOTE: *Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).*

NOTE: *37 C.F.R. 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.*

[ ] 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

10/030015
531 Rec'd PCT 31 DEC 2001

SIGNATURE OF PRACTITIONER

Reg. No.: 33,860

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DESCRIPTION

ADHESIVE PREPARATION FOR PERCUTANEOUS ABSORPTION

Technical Field

The present invention relates to an adhesive preparation for percutaneous absorption containing norethisterone dissolved in a base of the adhesive preparation which contains a styrene-isoprene-styrene block copolymer. Further, the present invention relates to an adhesive preparation for percutaneous absorption containing estradiol in a base in an amount of not more than 2 % by weight based on the whole base.

Background Art

In order to minimize an unnecessary metabolism of estradiol as well as to provide a therapeutic effect as a result of delivering a drug into blood effectively, trials for percutaneous administration have been performed. On the other hand, suppression of an adverse reaction of administered estradiol has also been tried by absorbing progestin percutaneously.

In JP-A-4-342532, a preparation for percutaneous absorption is proposed, which comprises, as main components, active ingredients comprising estradiol and progestin as well as an acrylic adhesive consisting of 2-ethylhexyl acrylate and N-vinyl-2-pyrrolidone as an adhesive. However, this preparation for percutaneous absorption has disadvantages because the acrylic adhesive shows a low drug releasability as well as too strong irritation to the skin to be used for a long term continuous administration. In the indication of existence of patent JP-A-6-510279, a

method for adjusting a saturated concentration of drug in a base by admixing a polymer having a different solubility parameter is proposed. However, this proposal has also a problem for a long term administration relating to the skin irritation due to use of an acrylate polymer as a polymer.

In addition, since norethisterone acetate generally admixed for percutaneous administration as a progestin has a higher compatibility with a base compared with norethisterone, a large amount of drug has to be admixed in the styrene-isoprene-styrene block copolymer base or the acrylic base in order to obtain a good permeability. Further, in order to obtain a therapeutically effective amount of permeation, a high concentration of norethisterone acetate should be admixed. Moreover, a large amount of drug is remained in a base of the adhesive preparation after applying to the skin. Consequently, it is less efficient in view of drug permeability and cost-effectiveness.

Disclosure of the Invention

In consideration of the above problems, an aspect of the present invention is to provide an adhesive preparation for percutaneous absorption intending:

1) a good percutaneous permeability of drug,

2) an effective use of drug in a base.

Further aspect of the present invention is to provide an adhesive preparation for percutaneous absorption, in which a therapeutically effective amount of drug can be correctly and securely released as well as less irritating to the skin after application of the adhesive preparation for percutaneous absorption to the skin of a patient.

As a result of an extensive study in order to solve the above problem, the present inventors found that a good skin permeability of drug and an efficient use of drug in a base could be achieved by admixing norethisterone except for the esters, the

derivatives and the salts thereof to a progestin, focusing on a relationship between solubility of a drug in a base and a skin permeability of a drug. Further, the inventors found that estradiol as a estrogen could also be admixed to the above admixure. In addition, the inventors found that an adhesive preparation having a good drug permeability into the skin, a good stability of formulation and a less skin irritation could be obtained by using a styrene-isoprene-styrene block copolymer, a softener and an adhesive agent as base components of an adhesive preparation for percutaneous absorption, and completed the present invention.

The present invention relates to an adhesive preparation for percutaneous absorption containing norethisterone dissolved in a base of the adhesive preparation which contains a styrene-isoprene-styrene block copolymer. More particularly, the present invention relates to the above adhesive preparation for percutaneous absorption having not less than 30 % of releasing rate of norethisterone in water after 24 hours, determined by the drug releasing test (according to the cylinder method described in the USP Drug Release 〈724〉 Test), which is conducted under the conditions of 900 ml of water for test solution; temperature of test solution, 32.0 ±0.5℃; distance from the lowest end of cylinder to the basal inner plane of vessel, 25 ± 2 mm; and rotation of cylinder, 50 rpm.

The present invention further relates to an adhesive preparation for percutaneous absorption comprising further containing estradiol in an amount not more than 2 % by weight based on the whole base.

Brief Description of Drawing

Fig. 1 shows the results of the releasing tests of estradiol (E2) on the adhesive preparation in Example 4 (▼), Comparative Example 1 (●) and Comparative Example

4 (■).

Fig. 2 shows the results of the releasing tests of norethisterone acetate (NETA) and norethisterone (NET) on the adhesive preparations in Example 4 (▼), Comparative Example 1 (●) and Comparative Example 4 (■).

Fig. 3 shows the results of the skin permeability tests of estradiol (slant lines), and norethisterone acetate (NETA) and norethisterone (NET) (dots) using hairless mice on the adhesive preparations in Example 4, Comparative Example 1, Comparative Example 2 and Comparative Example 5.

Best Mode for Carrying Out the Invention

The adhesive preparation for percutaneous absorption of the present invention is a preparation admixed with norethisterone except for the esters, the derivatives and the salts thereof, as a progestin of drug by dissolving in a base of the adhesive preparation. Further, an estrogen such as estradiol and other female sex hormones can be admixed, if necessary.

A high skin permeability, which could not be obtained by the conventional combination of a drug and a base, can be obtained at a low concentration of drug by a combination of norethisterone and base components containing a styrene-isoprene-styrene block copolymer (SIS) of the present invention.

Preferable amount of norethisterone to be admixed as a progestin used in the present invention is the amount at which norethisterone can exist in the base components in soluble state but not crystallized. In the present invention, a definition that the drug exist in soluble state in the base means a condition in which no crystallization of the drug is found in the base, and the drug can exist in any condition in the base so long as no crystallization is observed. A releasing rate of norethisterone in

the adhesive preparation for percutaneous absorption of the present invention increases in proportion to an increase in the concentration of norethisterone dissolved in the base components. However, since release of norethisterone deceases depending on an occurrence of crystallization, it is preferable to use at the concentration showing no crystallization.

A preferable amount of norethisterone to be dissolved in the present invention is in an amount not more than 2 % by weight, more preferably 0.1 - 2 % by weight.

Release of norethisterone of the adhesive preparation for percutaneous absorption of the present invention is affected by the base component. Consequently, the solubility of norethisterone can be determined by the drug releasability test. Preferable drug releasing test is a method for determining releasing rate of drug to the water. For example, the releasing test includes a test in which a releasing rate to water is measured after 24 hours under the conditions of test solution, 900 ml; temperature of test solution, 32.0 ± 0.5℃; and rotation of cylinder, 50 rpm. An amount of norethisterone to be dissolved in the adhesive preparation for percutaneous absorption of the present invention is the amount showing not less than 30 %, preferably not less than 40 % of releasing rate after 24 hours by this releasing test.

In the adhesive preparation for percutaneous absorption of the present invention, drugs other than norethisterone can be admixed. Other drugs to be admixed include an estrogen such as estradiol and other female sex hormones. Particularly, since estradiol has similar physico-chemical properties to those of norethisterone, it can be admixed at any ratio depending upon the therapeutic objectives, preferably in amount of 0.1 - 2 % by weight based on the whole base. A ratio of estradiol to norethisterone to be admixed can be determined within the range that the values of estradiol and norethisterone acetate converted to norethisterone show permeabilities similar to those

of the known adhesive preparation for percutaneous absorption of estradiol and norethisterone acetate.

An adhesive preparation for percutaneous absorption of the present invention uses a base containing a styrene-isoprene-styrene block copolymer (SIS). The base components preferably include a styrene-isoprene-styrene block copolymer, as well as softener and adhesive resin. Further, the base components of the present invention may include antioxidant, solubilizing agent and absorption enhancer if necessary, in addition to the above described base components.

A styrene-isoprene-styrene block copolymer includes styrene-isoprene-styrene block copolymer (Shell Chem. Corp., trade name: Califrex TR-1107; Califrex TR-1111), styrene-isoprene-styrene block copolymer (Nippon Synthetic Rubber Co. Ltd., trade name: JSR 5000, JSR 5100) and styrene-isoprene-styrene block copolymer (Nippon Zeon Co. Ltd., trade name: Quintac 3421). These polymers can be used in single or in combination of two or more types.

A softener includes liquid paraffin, polybutene, castor oil, cottonseed oil, palm oil, coconut oil and processed oil.

An adhesive resin includes alicyclic saturated hydrocarbon resin (e.g. Alcon P-100, trade name), rosin ester (e.g. KE-311; KE-100; super-ester S-100, trade name), hydrogen alicyclic hydrocarbon (e.g. Escolet 5300, trade name), terpene-based hydrogenated resin (e.g. Clearon P-105, trade name) and hydrogenated rosin ester (e.g. Foral 105, trade name).

The base components of the adhesive preparation for percutaneous absorption of the present invention can further contain, if necessary, other additives in order to maintain adhesion, safety and stability of the base. Concretely, an inorganic filler such as zinc oxide, calcium carbonate, titanium dioxide and silica and a solubilizing agent

such as crotamiton, polyisobutylene and dibutyl hydroxytoluene can be admixed properly in an appropriate amount.

Amounts of base components of the present invention to the whole base are as follows:

Styrene-isoprene-styrene block copolymer is 10 - 30 % by weight, preferably 13 - 27 % by weight, more preferably 15 - 25 % by weight; softener is 10 - 60 % by weight, preferably 12 - 55 % by weight, more preferably 15 - 50 % by weight; and adhesive resin is 20 - 60 % by weight, preferably 23 - 57 % by weight, more preferably 25 - 50 % by weight. These compounds can be combined at any ratio within these ranges.

If an amount of the styrene-isoprene-styrene block copolymer is less than the above ranges, cohesive force becomes insufficient, and if exceeds the ranges, it causes problems of poor adhesion as well as less flexibility of the preparation. If an amount of the softener is less than the above ranges, it causes problems of poor adhesion as well as less flexibility of the preparation, and if exceeds the ranges, cohesive force becomes insufficient. If an amount of the adhesive resin is less than the above ranges, it causes a trouble of poor adhesion, and if exceeds the ranges, it causes skin irritation such as corneous exfoliation at removal of the preparation from the skin.

In the base components of the adhesive preparation for percutaneous absorption of the present invention, necessary amounts of other components in addition to the above components may be admixed to prepare a required dosage form. The dosage form of the adhesive preparation for percutaneous absorption of the present invention is preferably plasters, particularly more preferably substantially anhydrous plasters.

The base containing drugs of the adhesive preparation for percutaneous

absorption of the present invention is preferably used by spreading on a support mean such as film. The film of the support mean in the present invention should have properties superior in barrier property in order to prevent leakage, volatility and adsorption of the drugs. Further, it is preferable to have a proper flexibility when the adhesive preparation for percutaneous absorption is applied on the skin. A material for the support mean is not specially limited, so long as it clears the above conditions. Concretely, it includes aluminum, ethylene-vinyl acetate copolymer or its saponified polymer, cellulose acetate, cellulose, nylon, polyester, polyethylene, poly(vinylidene chloride), polycarbonate, poly(vinyl alcohol) and polypropylene. These materials are processed to a film or, if necessary, to a laminate with paper or cloth or to a laminated film, as well as a film treated with vapor deposition of aluminum or silica to improve barrier property.

In the adhesive preparation for percutaneous absorption of the present invention, a film for removal liner layer may be provided on the opposite side of the supporting mean. The film for removal liner layer should be able to block leakage and volatility of the drugs from the drug layer during storage of the adhesive preparation for percutaneous absorption. In addition, the removal liner layer has to be removable when it is used on a machine. A material for the removal liner layer is aluminum, cellulose, polyester, polyethylene and polypropylene, and if necessary, these films may be laminated. Further, the surface thereof may be treated with silicon or fluorocarbon, or known additives may be admixed with the liner material to adjust removability or barrier property. In order to make handling for removal easy, the removal liner may be provided with a tab for removal.

Subsequently, a process for manufacturing the adhesive preparation for percutaneous absorption of the present invention will be explained. The adhesive

preparation for percutaneous absorption of the present invention can be manufactured, for example, by dissolving all base components excluding drugs under heating, then adding drug components and mixing them homogeneously, and as occasion demands, spreading the mixture on the above described supporting mean followed by covering with a liner, then cutting into a desired form to obtain a product, or spreading the mixture on a film applied with a removal treatment, then transferring the mixture to a suitable supporting mean under a pressure to obtain a product. Alternatively, the adhesive preparation for percutaneous absorption can be manufactured by dissolving all components in an organic solvent such as hexane, toluene and ethyl acetate, then spreading the mixture on the above supporting mean, followed by covering with a liner after removing the organic solvent, then cutting into a desired form to obtain a product, or spreading the mixture on a film applied with a removal treatment, then transferring the mixture to a suitable supporting mean under a pressure after removing the solvent to obtain a product.

Hereinbelow, the adhesive preparation for percutaneous absorption of the present invention will be explained in detail by illustrating examples and experimental examples but the present invention is not limited within these examples.

Examples

Numerical values in the examples and comparative examples are given by a percent by weight.

Example 1

Styrene-isoprene-styrene block copolymer	10
Liquid paraffin	60
Adhesive agent (alicyclic satureted hydrocarbon resin, trade name: Alcon P-100)	20
Polyisobutylene	8.8
Dibutyl hydroxytoluene	1
Estradiol	0.1
Norethisterone	0.1

A preparation was manufactured in this formulation according to the above manufacturing method and a product was cut in a desired size to obtain a mixed preparation of estradiol and norethisterone.

Example 2

Styrene-isoprene-styrene block copolymer	30
Liquid paraffin	10
Adhesive agent (rosin ester, trade name: KE-311)	35
Polyisobutylene	10
Crotaminton	10
Dibutyl hydroxytoluene	1
Estradiol	2
Norethisterone	2

A preparation was manufactured in this formulation according to the above manufacturing method and a product was cut in a desired size to obtain a mixed preparation of estradiol and norethisterone.

Example 3

Styrene-isoprene-styrene block copolymer	20
Liquid paraffin	25
Adhesive agent (hydrogenated rosin ester, trade name: Foral 105)	30
Polyisobutylene	12
Crotamiton	10
Dibutyl hydroxytoluene	1
Estradiol	1.5
Norethisterone	0.5

A preparation was manufactured in this formulation according to the above manufacturing method and a product was cut in a desired size to obtain a mixed preparation of estradiol and norethisterone.

Example 4

Styrene-isoprene-styrene block copolymer	25
Liquid paraffin	30
Adhesive agent (hydrogenated rosin ester, trade name: Foral 105)	25
Polyisobutylene	10
Crotamiton	8
Dibutyl hydroxytoluene	1
Estradiol	0.5
Norethisterone	0.5

A preparation was manufactured in this formulation according to the above manufacturing method and a product was cut in a desired size to obtain a mixed

preparation of estradiol and norethisterone.

Example 5

Styrene-isoprene-styrene block copolymer	15
Liquid paraffin	15
Adhesive agent (hydrogenated rosin ester, trade name: Foral 105)	60
Polyisobutylene	6.6
Hexylene glycol	1
Dibutyl hydroxytoluene	1
Estradiol	0.7
Norethisterone	0.7

A preparation was manufactured in this formulation according to the above manufacturing method and a product was cut in a desired size to obtain a mixed preparation of estradiol and norethisterone.

Comparative Example 1

Styrene-isoprene-styrene block copolymer	25
Liquid paraffin	30
Adhesive agent (hydrogenated rosin ester, trade name: Foral 105)	25
Polyisobutylene	10
Crotamiton	8
Dibutyl hydroxytoluene	1
Estradiol	0.5
Norethisterone acetate	0.5

A preparation was manufactured in this formulation according to the above

manufacturing method and a product was cut in a desired size to obtain a mixed preparation of estradiol and norethisterone acetate.

Comparative Example 2

Styrene-isoprene-styrene block copolymer	25
Liquid paraffin	24.5
Adhesive agent (hydrogenated rosin ester, trade name: Foral 105)	25
Polyisobutylene	10
Crotamiton	8
Dibutyl hydroxytoluene	1
Estradiol	0.5
Norethisterone acetate	6

A preparation was manufactured in this formulation according to the above manufacturing method and a product was cut in a desired size to obtain a mixed preparation of estradiol and norethisterone acetate.

Comparative Example 3

Styrene-isoprene-styrene block copolymer	25
Liquid paraffin	25.5
Adhesive agent (hydrogenated rosin ester, trade name: Foral 105)	25
Polyisobutylene	10
Crotamiton	8
Dibutyl hydroxytoluene	1
Estradiol	0.5
Norethisterone acetate	5

A preparation was manufactured in this formulation according to the above manufacturing method and a product was cut in a desired size to obtain a mixed preparation of estradiol and norethisterone acetate.

Comparative Example 4

Styrene-isoprene-styrene block copolymer	30
Liquid paraffin	10
Adhesive agent (hydrogenated rosin ester, trade name: Foral 105)	35
Polyisobutylene	9
Crotamiton	10
Dibutyl hydroxytoluene	1
Estradiol	2.5
Norethisterone	2.5

A preparation was manufactured in this formulation according to the above manufacturing method and a product was cut in a desired size to obtain a mixed preparation of estradiol and norethisterone.

Comparative Example 5 (acrylate base)

TS-620 (methyl acrylate - 2-ethylhexyl acrylate copolymer resin emulsion: Nippon Carbide Co., Ltd.)	91
Crotamiton	8
Estradiol	0.5
Norethisterone	0.5

A preparation was manufactured in this formulation according to the above

manufacturing method and a product was cut in a desired size to obtain a mixed preparation of estradiol and norethisterone.

Experimental Example 1. Confirmation on solubility of drugs by crystallization

Appearances of crystals were observed on the test pieces obtained in Examples 1, 2, 3, 4 and 5, and also Comparative Examples 2, 3 and 4 at the initial time, after stored at 25℃ for 6 months and after stored at 40℃ for 6 months. Results are shown in Table 1.

Table 1

	Initial Time	After the storages for 6 months	
		25℃	40℃
Example 1	No Crystallization	No Crystallization	No Crystallization
Example 2	No Crystallization	No Crystallization	No Crystallization
Example 3	No Crystallization	No Crystallization	No Crystallization
Example 4	No Crystallization	No Crystallization	No Crystallization
Example 5	No Crystallization	No Crystallization	No Crystallization
Comparative Example 2	No Crystallization	Crystallized	Crystallized
Comparative Example 3	No Crystallization	No Crystallization	No Crystallization
Comparative Example 4	No Crystallization	Crystallized	Crystallized

Although crystallization was not observed at the initial time, but was observed

after the storages at 25℃ for 6 months and at 40℃ for 6 months in Comparative Examples 2 and 4.

According to Comparative Example 2, it was found that admixing of norethisterone acetate should be in an amount less than 6 % by weight for preventing crystallization. Further, since the crystallization was also observed in Comparative Example 4, it was indicated that admixing of norethisterone should be in an amount not more than 2 % by weight for preventing crystallization.

In conclusion, it can be understood that if an amount of norethisterone admixed in the base is in an amount not more than 2 % by weight, norethisterone is completely dissolved in the base.

Experimental Example 2. (Releasing test)

Drug releasabilities were tested on the test pieces obtained in Example 4, Comparative Example 1 and Comparative Example 4 (after crystallization) according to the cylinder method described in the USP Drug Release 〈724〉 Test under the following conditions.

Test solution	900 ml water
Temperature of test solution	32.0 ± 0.5℃
Distance from the lowest end of cylinder to the basal inner plane of vessel	25 ± 2 mm
Rotation of cylinder	50 rpm

Test results of estradiol (E2) are shown in Fig. 1 and those of norethisterone acetate (NETA) in Comparative Example 1 and norethisterone (NET) in Comparative Example 4 are shown in Fig. 2, respectively. As a progestin, 0.5 % of norethisterone in Example 4 and 0.5 % of norethisterone acetate in Comparative Example 1 were

admixed, respectively. In spite of the identical concentrations of the drugs were used in the tests, a good releasing rate of progestin after 24 hours showing 30 % or more could be obtained only with the test piece from Example 4. In Comparative Example 4, decreases in the releases of drugs caused by crystallizations of estradiol and norethisterone were observed.

Experimental Example 3. (Skin permeability test)

Dorsal skin permeability tests of hairless mice (7 weeks old, female) were conducted at 37℃ using Franz's diffusion cell on the test pieces obtained in Example 4, Comparative Example 1, Comparative Example 2 and Comparative Example 5. After initiation of the test, a receptor solution was collected at certain times, and immediately thereafter, the receptor solution was supplemented, then an amount of the drug permeated to the collected receptor solution was assayed by means of high performance liquid chromatography. Numbers of samples in each test piece were 3 pieces, respectively.

Results are shown in Fig. 3. In Fig. 3, columns with slant lines show estradiol (E2) and those of dots show norethisterone (NET) or norethisterone acetate (NETA), respectively. With respective to Example 4 and Comparative Example 2, despite of the high concentration of progestin in Comparative Example 2, the skin permeabilities were in the equivalent level. In Comparative Example 1 wherein the progestin concentration was made equal to that in Example 4, the permeability of norethisterone acetate resulted in a considerably low level. The drugs in Comparative Example 5 using the acrylate base exhibited much lower drug permeability than the drugs in Example 4.

A distribution coefficient between a skin and a base is known as one of factors to determine a skin permeation rate of a drug. A high distribution coefficient can be

obtained by enlarging the difference in solubility parameters between a drug and a base component. Consequently, it is necessary to select a base having a solubility parameter distant from the drug and to apply a drug having a solubility parameter close to the skin. In the adhesive preparation for percutaneous absorption of the present invention, the superior results seemed to be obtained in the skin permeability test, since a high distribution coefficient could be obtained by combining with the base.

Industrial Applicability

The adhesive preparation for percutaneous absorption of the present invention has an effect showing a high skin permeability at a low drug concentration. In addition, as the result of using norethisterone except for the esters, the derivatives and the salts thereof, excess dissolving of the drug to a base can be prevented as well as maintaining proper permeability. Further, with the adhesive preparation for percutaneous absorption of the present invention, programmed amounts of progestin and estrogen can be applied to a patient accurately and securely at the lower drug contents than in the conventional adhesive preparation for percutaneous absorption.

Moreover, since the adhesive preparation for percutaneous absorption of the present invention has a high degree of freedom in its composition, a proper design of dosage form in compliance with conditions can be made by considering its efficacy and stability.

CLAIMS

1. An adhesive preparation for percutaneous absorption containing norethisterone dissolved in a base of the adhesive preparation which contains a styrene-isoprene-styrene block copolymer.

2. The adhesive preparation for percutaneous absorption according to claim 1, wherein an amount of norethisterone to be dissolved is the amount to show the releasing rate in water being not less than 30 % after 24 hours determined by the drug releasing test (according to the cylinder method described in the USP Drug Release 〈724〉 Test), which is conducted under the conditions of water for test solution, 900 ml; temperature of test solution, 32.0 ±0.5℃; distance from the lowest end of cylinder to the basal inner plane of vessel 25 ± 2 mm; and rotation of cylinder, 50 rpm.

3. The adhesive preparation for percutaneous absorption according to any of claims 1 - 2, wherein an amount of norethisterone to be dissolved is in the amount not more than 2 % by weight based on the whole base.

4. The adhesive preparation for percutaneous absorption according to any of claims 1 – 3, comprising further containing estradiol in an amount not more than 2 % by weight based on the whole base.

5. The adhesive preparation for percutaneous absorption according to any of claims 1 – 4, wherein the adhesive preparation containing a styrene-isoprene-styrene block copolymer comprises 10 - 30 % by weight of a styrene-isoprene-styrene block copolymer, 10 - 60 % by weight of a softener and 20 - 60 % by weight of an adhesive resin based on the whole base.

ABSTRACT

An adhesive preparation for percutaneous absorption in which high drug permeability at a low drug concentration and satisfactory drug stability have been obtained by regulating the solubility of a drug in a base. The adhesive preparation comprises a base comprising a styrene-isoprene-styrene block copolymer and norethisterone contained in the base. Preferably, the drug is dissolved in the base in an amount of up to 2 wt.% based on the whole base.

10/030015

Fig. 1

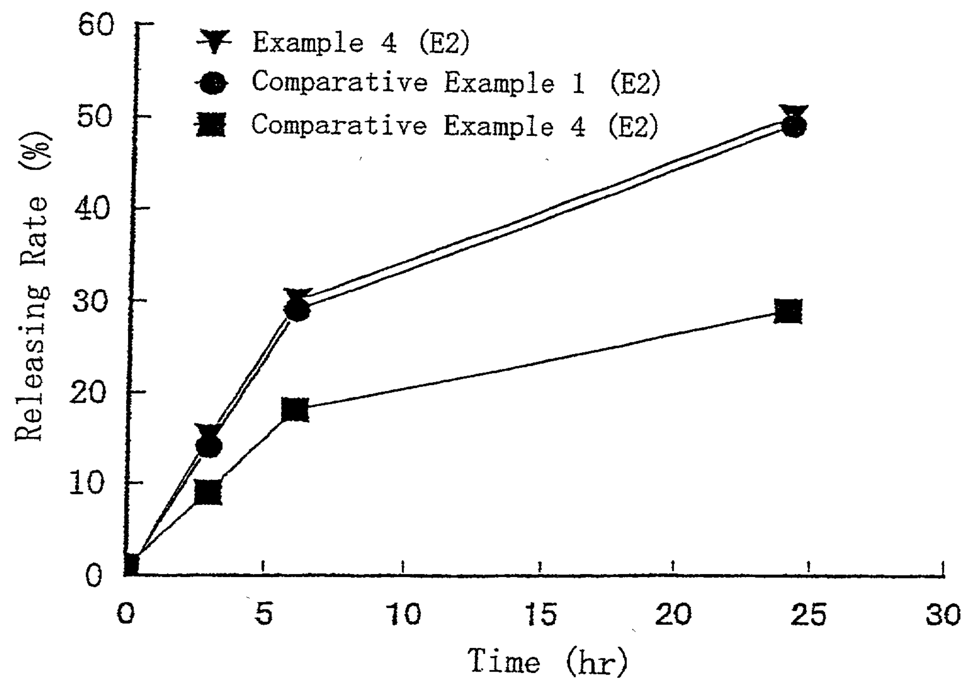


Fig. 2

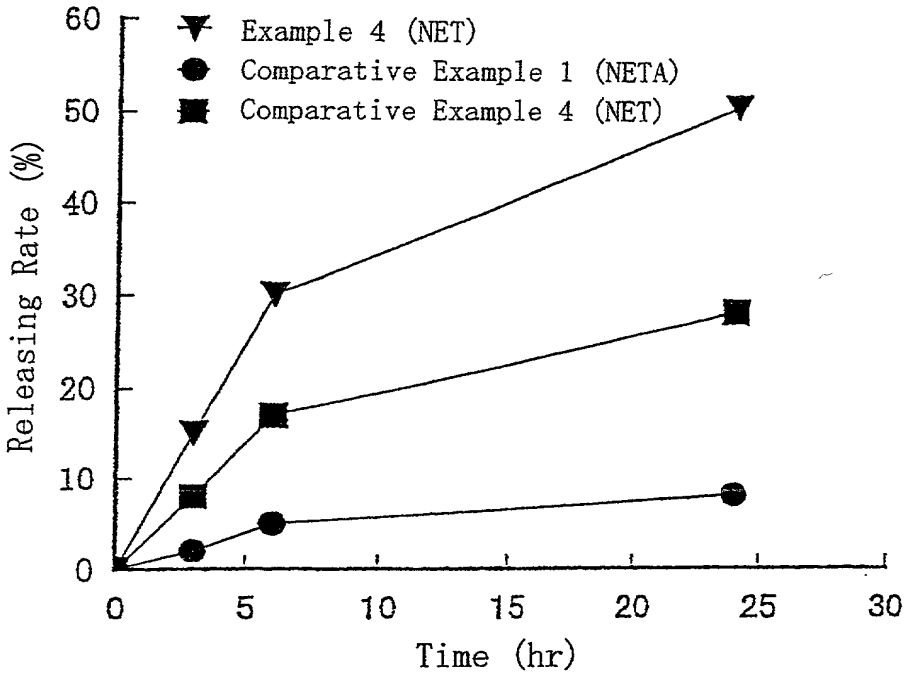
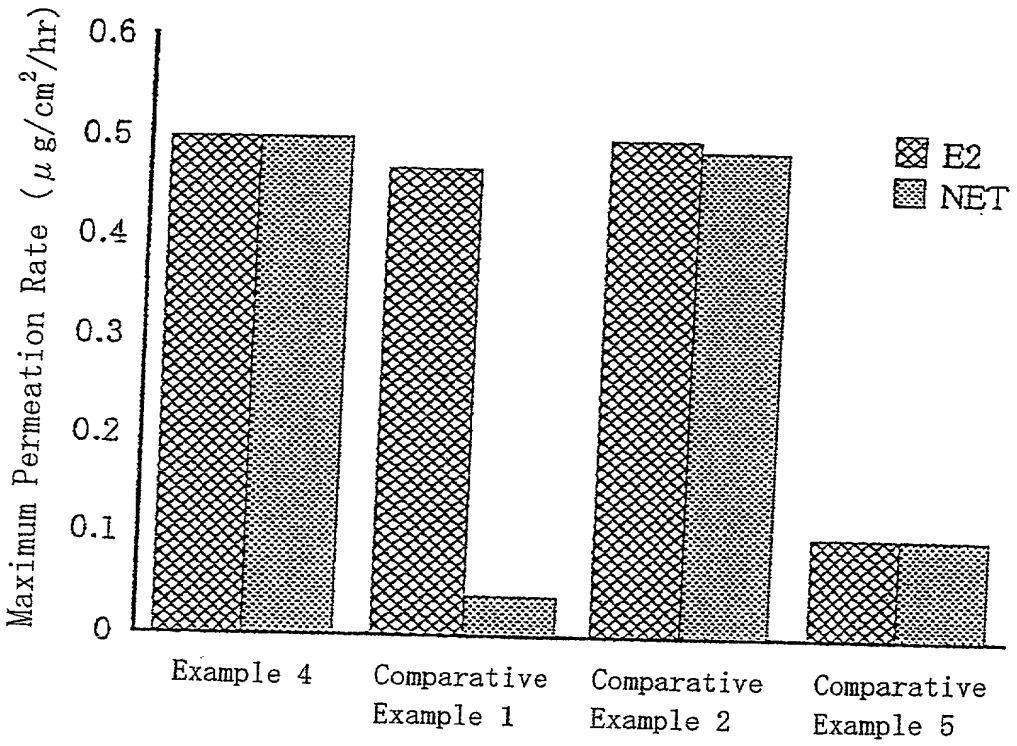

Example 4 (NET)
Comparative Example 1 (NETA)
Comparative Example 4 (NET)
Releasing Rate (%)
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time (hr)

Fig. 3


Maximum Permeation Rate (μg/cm^2/hr)
0.6
0.5
0.4
0.3
0.2
0.1
0
E2
NET
Example 4
Comparative Example 1
Comparative Example 2
Comparative Example 5

56687 (71526)

Express Mail Label No.

Docket No. 56687 (71526)

Declaration and Power of Attorney for Patent Application
English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"ADHESIVE PREPARATION FOR PERCUTANEOUS ABSORPTION"

the specification of which

(check one)

[ ] is attached hereto.
[X] was filed on December 31, 2001 as United States Application No. or PCT Application No. 10/030,015
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
11-187415/1999 (Number)	Japan (Country)	01 July 1999 (Day/Month/Year Filed)	[ ]
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	[ ]
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	[ ]

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. Section 120 of the United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark office all information known to me to be material to patentability as defined in Title 37, C.F.C., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
PCT/JP00/04361	30 June 2000	Pending

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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